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Review

# Rheumatoid arthritis–celiac disease relationship: Joints get that gut feeling☆

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ABSTRACT

Rheumatoid arthritis (RA) and celiac disease (CD) belong to the autoimmune disease family. Despite being separate entities they share multiple aspects. Epidemiologically they share comparable incidence environmental influences, associated antibodies and a recent incidental surge. They differ in their HLA pre-dispositions and specific predictive and diagnostic biomarkers. At the clinical level, celiac disease exhibits extra-intestinal rheumatic manifestations and RA gastrointestinal ones. Small bowel pathology exists in rheumatic patients. A trend towards responsiveness to a gluten free diet has been observed, ameliorating celiac rheumatic manifestations, whereas dietary interventions for rheumatoid arthritis remain controversial.

Pathophysiologically, both diseases are mediated by endogenous enzymes in the target organs. The infectious, dysbiotic and increased intestinal permeability theories, as drivers of the autoimmune cascade, apply to both diseases.

Contrary to their specific HLA pre-disposition, the diseases share multiple non-HLA loci. Those genes are crucial for activation and regulation of adaptive and innate immunity. Recently, light was shed on the interaction between host genetics and microbiota composition in relation to CD and RA susceptibility, connecting bugs and us and autoimmunity.

A better understanding of the above mentioned similarities in the gut–joint inter-relationship, may elucidate additional facets in the mosaic of autoimmunity, relating CD to RA.



**Contents**



*Abbreviations:* RA, rheumatoid arthritis; CD, celiac disease; RF, rheumatoid factor; tTg, tisue transglutaminase; anti-CCP, anticyclic citrullinated protein; ACPAs, antibodies to citrullinated protein antigens; PAD, peptidylarginine deiminase.

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## 1. Introduction

### 1.1. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic, chronic inflammatory, autoimmune disorder that results in joint destruction and is associated with progressive disability and various systemic complications. It is characterized by persistent synovitis, systemic inflammation, and autoantibodies. Around 50% of the risks of developing rheumatoid arthritis are attributable to genetic factors. Smoking is the main environmental risk. In industrialized countries, rheumatoid arthritis affects 0.5–2.0% of adults, with 5–50 per 100,000 new cases annually. The disorder is most typical in women and elderly people. Although RA manifestation includes pain, stiffness, swelling, and functional impairment, it can be difficult to diagnose in the early stages, as its symptoms can closely mimic other diseases [1]. The genetic predisposition is related to human leukocyte antigen HLA DRB1 haplotypes, but 50 associated loci have been described. Despite unknown etiology, enhanced understanding of molecular pathogenesis has enabled development of innovative biological agents that target specific parts of the immune system. New knowledge has emerged of how environmental factors interact with susceptibility genes and the immune system in the pathogenesis of a major subset of rheumatoid arthritis [2–5].

### 1.2. Celiac disease

Celiac disease (CD) is an autoimmune disorder precipitated in genetically predisposed individuals by the ingestion of prolamin, a major storage protein found in wheat, rye, barley and oats [6]. The genetic predisposition is related to HLA DQ2 and DQ8 haplotypes, but more than 60 associated loci have been described. It affects 0.5 to 1.0% of the population worldwide, with large differences between European countries [7]. We are currently witnessing an epidemiological shift in the disease phenotype towards a more advanced age, and increased prevalence of latent, hyposymptomatic or asymptomatic behavior, an attestation of the importance of serological biomarkers in disease screening and diagnosis [8]. It has been shown that the classic intestinal clinical picture of malnutrition, chronic diarrhea and nutritional deficiencies are disappearing and extra intestinal presentations are emerging. Skin, endocrine, skeletal, hepatic, hematological, thrombophilic, gynecological, fertility, dental, psychiatric and behavioral abnormalities are often described [9–12]. The sequential chain of events in disease development is continuously being unraveled and may lead to future therapeutic strategies [13,14]. Here we review the multifaceted similarities between the two autoimmune diseases, RA and CD. Updates on the multiple innovative aspects associated with the interplay between environmental factors like nutrients/microbes, genetic susceptibility and protection, intestinal dysbiosis and permeability and RA and CD development, are presented. Updating and expanding our knowledge of both diseases presents a window of opportunity for the development of novel therapeutic strategies and provides new hope for patients.

## 2. Similarities and dissimilarities between CD and RA

### 2.1. Epidemiology

A review of the medical literature reveals that the association between CD and RA has been well described in individual cases, in screening of patient populations and genetic backgrounds [15]. Table 1 summarizes the main epidemiological similarities and differences between the two conditions. The incidences and the geoepidemiological trends are comparable. The female gender predominates in both diseases, but much more so in RA. They differ substantially in the environmentally associated inducers. RA is more prevalent postpartum and in smokers [1]. The brain–gut axis is involved in many gastrointestinal conditions and stressful events alter the functions of the digestive tract and stressful stimuli breach intestinal functional integrity [16,17]. Before diagnosis, the number of stressful events in celiac disease was found to be more frequent than in the control group suggesting that life events may favor the clinical appearance of celiac disease or accelerate its diagnosis[18]. Similarly, stress is associated with RA and it was shown recently, that mindfulness-based stress decrease, reduced RA disease activity indices [19]. The exact etiopathogenesis of RA is not clear despite the many studies devoted to it. Several infections are believed to trigger RA and CD autoimmunity. In RA certain viral infections like parvovirus B19, hepatitis c virus and EBV are considered initializing factors for RA. Clinical and animal model studies have suggested that infections by many microorganisms, such as *Porphyromonas gingivalis*, *Proteus*

**Table 1**
Rheumatoid arthritis and celiac disease similarities and dissimilarities.

| | Celiac disease | Rheumatoid arthritis |
|---|---|---|
| Incidence | 1% | 1% |
| Female predominance | + | ++ |
| Geoepidemiology | North-west to south-east gradient | North-west to south-east gradient |
| Environmental factors | Gluten, mTG, infections, stress, formula feed, increased diversity of dysbiosis | Infections, Porphyromonas gingivalis, increased diversity of dysbiosis, stress, smoking, Postpartum period, oral contraceptive pill, caffeine |
| Virus | EBV, HCV, tuberculosis | EBV, HCV, tuberculosis |
| HLA predisposition | DQ-2, DQ-8 | DRB1, "shared epitope" HLADR "01, 04, PTNP22" |
| Anti-gliadin/anti-tTg/anti-neo-epitope antibodies | Non-specific/specific | Non-specific/non-specific (epiphenomenon) |
| Inducer enzymes, posttranslational modification | tTg, mTg. Deamidation, cross-linking | Tissue PAD, mPAD. Deimination–citrullination, carbamylilation |
| Biomarkers (predictive, diagnostic) | Anti-tTg/neo-epitope tTg antibodies | Anti-citrullinated, anti-carbamylated protein antibodies |
| Adaptive and innate immunity | +++ | +++ |
| Intestinal inflammation | ++ | ++ |
| Target/associated organs | Small bowel/joint, bone, endocrine, heart, lung, brain, nerve, skin, pancreas | Joints/intestine, bone, endocrine, heart, lung, brain, nerve, vessels |

+, low; ++, moderate; +++, high.